

## CHRONIC TOXICITY SUMMARY

# PROPYLENE OXIDE

(1,2-propylene oxide; methyl ethylene oxide; propene oxide)

CAS Registry Number: 75-56-9

### I. Chronic Toxicity Summary

<i>Inhalation reference exposure level</i>	<b>30 µg/m<sup>3</sup> (9 ppb)</b>
<i>Critical effect(s)</i>	Degenerative and hyperplastic changes in the respiratory epithelium of rats
<i>Hazard index target(s)</i>	Respiratory system

### II. Physical and Chemical Properties (HSDB, 1994)

<i>Description</i>	Colorless liquid
<i>Molecular formula</i>	C <sub>3</sub> H <sub>6</sub> O
<i>Molecular weight</i>	58.08
<i>Density</i>	0.83 g/cm <sup>3</sup> @ 20° C
<i>Boiling point</i>	34.23° C
<i>Melting point</i>	-112.13° C
<i>Vapor pressure</i>	445 torr @ 20° C
<i>Solubility</i>	Soluble in water, miscible in acetone, benzene, carbon tetrachloride, methanol, ether
<i>Conversion factor</i>	2.38 mg/m <sup>3</sup> per ppm at 25° C

### III. Major Uses or Sources

Propylene oxide is used as a fumigant such as in the sterilization of packaged foods. It is also used as a chemical intermediate in the production of propylene glycol and glycol ethers and as a solvent. Propylene oxide is used in the preparation of surfactants and oil demulsifiers (HSDB, 1994). The annual statewide emissions from facilities reporting under the Air Toxics Hot Spots Act in California, based on the most recent inventory, were estimated to be 619,494 pounds of propylene oxide.

### IV. Effects of Human Exposures

Conclusive data regarding the effects of occupational exposure to propylene oxide were not located.

An epidemiological study examining mortality among workers with exposure to asbestos and several chemicals, including propylene oxide, identified three deaths due to mesothelioma, a rare cancer associated with asbestos exposure, and a statistically significant increase in the number of deaths attributed to forms of heart disease other than ischemia and hypertension (Egedahl *et al.*, 1989). The latter finding was explained by the authors to be the result of differences in diagnostic accuracy between rural and urban, and primary and tertiary medical care settings. A statistically significant decrease in observed deaths was found for all respiratory cancers, cancer of the bronchus and lung, circulatory disease, digestive diseases, cirrhosis and other liver disease, and death due to accidents, poisonings, and violence. These observations may be partially attributed to a “healthy worker effect”.

## **V. Effects of Animal Exposures**

Male and female rats were exposed for 124 or 123 weeks (respectively) to 30, 100 or 300 ppm propylene oxide 6 hours per day, 5 days per week (Kuper *et al.*, 1988). Interim sacrifices were performed at 12, 18, and 24 months. Cumulative mortality was statistically significantly different from controls at 115 weeks in rats of both sexes exposed to 300 ppm propylene oxide. Cumulative mortality was also significantly different from controls at 119 weeks in female rats exposed to 100 ppm. However, a contributing factor to the increased mortality in female rats was the presence of mammary tumors. Atrophy of the olfactory epithelium and degenerative changes in the respiratory epithelium were observed in both male and female rats following 28 months of exposure to 30, 100, or 300 ppm propylene oxide. Severe hyperplastic changes in the olfactory epithelium were observed in male and female rats following 28 months exposure to 300 ppm propylene oxide. Mild hyperplastic changes were observed in the olfactory epithelium of female rats exposed to 100 ppm propylene oxide.

Rats and mice were exposed to 200 and 400 ppm propylene oxide 6 hours per day, 5 days per week for 103 weeks (NTP, 1985). Survival in mice was adversely affected in all groups exposed to propylene oxide; a statistically significant decrease in survival was observed in male and female mice exposed to 400 ppm propylene oxide. Survival in rats was not adversely affected by propylene oxide exposure. Rats exhibited exposure-related increases in suppurative inflammation of the nasal cavity, epithelial hyperplasia and squamous metaplasia.

Rats were exposed to 1500 ppm propylene oxide 6 hours per day, 5 days per week for 7 weeks (Ohnishi *et al.*, 1988). After 3-4 weeks of exposure the rats exhibited an awkward gait; the rats were ataxic by the seventh week. Histopathological examination revealed axonal degeneration of myelinated fibers of the hindleg nerve and fasciculus gracilis indicating central-peripheral distal axonopathy.

Eldridge *et al.* (1995) exposed male F344 rats to 0, 10, 20, 50, 150, or 525 ppm propylene oxide vapor for up to 4 weeks (with up to 4 weeks of recovery). Histopathology showed that the incidence and severity of respiratory epithelial hyperplasia increased with exposure time and regressed after termination of exposure, with complete recovery after 4 weeks. Cell proliferation (determined by bromodeoxyuridine incorporation) was elevated following 1 and 4 weeks of exposure, but decreased to control values after 1 week of recovery. Degeneration of the

olfactory epithelium was found after 4 weeks of exposure with a decrease in incidence and severity after termination of exposure. Proliferation of olfactory epithelium was elevated during the 4-week exposure period and 1 week post-exposure and returned to control values after 4 weeks of recovery. The authors report a 4-week NOAEL for propylene oxide effects in nasal epithelium of 50 ppm.

Artificially inseminated rabbits were exposed to 500 ppm propylene oxide on days 1-19 or 7-19 of gestation (Hardin *et al.*, 1983). Maternal toxicity as indicated by a significant reduction in food intake and a significant decrease in maternal body weight gain was observed in both exposed groups. An increased number of resorptions per litter, with no change in total resorptions, was observed in rabbits exposed on days 1-19 of gestation. Sternebral and limb anomalies (considered minor by U.S. EPA and the authors) were significantly increased in the offspring of rabbits exposed on days 1-19 of gestation.

The same study also reported similar findings in sperm-positive rats exposed to 500 ppm propylene oxide on either days 1-16 or 7-16 of gestation or daily for 3 weeks prior to mating and then daily on days 1-16 of gestation. Reproductive capacity was impaired in rats exposed prior to breeding; the number of corpora lutea, implantation sites, and live fetuses were reduced. Those dams exposed pregestationally to propylene oxide also exhibited more resorptions. Maternal toxicity as indicated by decreased food intake and decreased body weight gain was observed in all exposed rats. Significant reductions in fetal body weight and fetal crown-rump length were observed in all exposed groups. An increased incidence of wavy ribs and reduced ossification were observed in the offspring of rats exposed from days 1-16 of gestation.

Harris *et al.* (1989) evaluated the developmental toxicity potential of propylene oxide in Fischer 344 rats. Four groups of 25 mated female rats were exposed to 0, 100, 300, and 500 ppm for 6 hours per day on gestation days 6 through 15. Cesarean sections were performed on all females on gestation day 20 and the fetuses were removed for morphological evaluation. Exposure to propylene oxide did not adversely affect survival, appearance, or behavior at any level. Maternal body weight gain and food consumption were reduced significantly at the 500 ppm level during exposure. Only one exposure-related effect was noted with respect to maternal water consumption, organ weights, cesarean section, or fetal morphological observations: increased frequency of seventh cervical ribs in fetuses at the maternally toxic exposure level of 500 ppm. Thus 300 ppm was considered the NOAEL.

## VI. Derivation of Chronic REL (U.S. EPA Reference Concentration (IRIS, 1995))

<i>Study</i>	Kuper <i>et al.</i> , 1988
<i>Study population</i>	Rats (male and female)
<i>Exposure method</i>	Inhalation (0, 30, 100 or 300 ppm)
<i>LOAEL</i>	30 ppm
<i>Critical effects</i>	Degenerative and hyperplastic changes in the respiratory epithelium
<i>NOAEL</i>	Not observed
<i>Exposure continuity</i>	6 hr/day for 5 days/week
<i>Exposure duration</i>	124 weeks
<i>Average experimental exposure</i>	5.4 ppm for LOAEL group (30 x 6/24 x 5/7)
<i>Human equivalent concentration</i>	1.2 ppm for LOAEL group (gas with extrathoracic respiratory effects, RGDR = 0.23, based on MV = 0.3 m <sup>3</sup> /day, SA(ET) = 11.6 cm <sup>2</sup> )
<i>LOAEL uncertainty factor</i>	3 (mild effects only observed during last 4 months of exposure)
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	3
<i>Intraspecies uncertainty factor</i>	10
<i>Cumulative uncertainty factor</i>	100
<i>Inhalation reference exposure level</i>	0.009 ppm (9 ppb, 0.03 mg/m <sup>3</sup> , 30 µg/m <sup>3</sup> )

## VII. Data Strengths and Limitations for Development of the REL

The chronic REL is equivalent to the US EPA RfC. The major strength of the REL for propylene oxide is the use of a well-conducted, long-term, multi-concentration study with adequate histopathological analyses. Weaknesses include the lack of adequate human data and the lack of a chronic NOAEL observation.

## VIII. References

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